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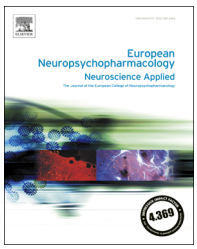

LSD modulates music-induced imagery via changes in parahippocampal connectivity

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Abstract
Psychedelic drugs such as lysergic acid diethylamide (LSD) were used extensively in psychiatry in the past and their therapeutic potential is beginning to be re-examined today. Psychedelic psychotherapy typically involves a patient lying with their eyes-closed during peak drug effects, while listening to music and being supervised by trained psychotherapists. In this context, music is considered to be a key element in the therapeutic model; working in synergy with the drug to evoke therapeutically meaningful thoughts, emotions and imagery. The underlying mechanisms involved in this process have, however, never been formally investigated. Here we studied the interaction between LSD and music-listening on eyes-closed imagery by means of a placebo-controlled, functional magnetic resonance imaging (fMRI) study. Twelve healthy volunteers received intravenously administered LSD (75 μg) and, on a separate occasion, placebo, before

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being scanned under eyes-closed resting conditions with and without music-listening. The parahippocampal cortex (PHC) has previously been linked with (1) music-evoked emotion, (2) the action of psychedelics, and (3) mental imagery. Imaging analyses therefore focused on changes in the connectivity profile of this particular structure. Results revealed increased PHC-visual cortex (VC) functional connectivity and PHC to VC information flow in the interaction between music and LSD. This latter result correlated positively with ratings of enhanced eyes-closed visual imagery, including imagery of an autobiographical nature. These findings suggest a plausible mechanism by which LSD works in combination with music listening to enhance certain subjective experiences that may be useful in a therapeutic context.
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1. Introduction

Humans have chosen to alter their consciousness via psychedelic drugs for millennia, and often in combination with music (Nettl, 1956). In the 1950s and 1960s, psychedelic drugs such as lysergic acid diethylamide (LSD) were used in psychotherapy, and modern clinical trials are re-examining their therapeutic potential (Bogenschutz et al., 2015; Gasser et al., 2014; Grob et al., 2011; Johnson et al., 2014). Since the inception of psychedelic-assisted psychotherapy, music-listening has been considered an important component in the therapeutic model (Bonny and Pahnke, 1972). It is believed that music acts synergistically with the drug to enhance emotionality, mental imagery, and access to personal memories (Bonny and Pahnke, 1972; Grof, 1980; Kaelen et al., 2015).[1] The main aim of the present study was to investigate the brain mechanisms underlying the effects of LSD and music on mental imagery.

The characteristic subjective effects of LSD and other psychedelics such as psilocybin are thought to depend on agonist actions at the serotonin 2A receptor (Glennon et al., 1984; Vollenweider et al., 1998). The serotonin 2A receptor is expressed on "excitatory" deep layer pyramidal cells, as well as on a smaller proportion of "inhibitory" interneurons (Andrade, 2011; Celada et al., 2013). Its activation depolarises the cell membrane of the host neuron, increasing its likelihood of firing (Aghajanian and Marek, 1999). Although expressed throughout the neocortex (Pazos et al., 1987), the serotonin 2A receptor is especially highly expressed in high-level association cortices, including the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC) and insula, but also in the visual cortex (VC) and, to a lesser extent, the entorhinal cortex (Erritzoe et al., 2009; Ettrup et al., 2014; Pazos et al., 1987). Not surprisingly, functional neuroimaging studies revealed altered activity in these brain regions during serotonin 2A receptor agonist-induced psychedelic states (Carhart-Harris et al., 2012a; Muthukumaraswamy et al., 2013; Riba et al., 2002; Vollenweider et al., 1997).

Of particular interest to the present study are the effects of psychedelics and music-listening on activity in the parahippocampal cortex (PHC). The PHC is an important hub within the medial temporal lobe (MTL) (Burwell, 2000; Eichenbaum and Lipton, 2008), and it's acute functioning is appreciably altered by psychedelics as determined by fMRI (Kometer et al., 2015; Tagliazucchi et al., 2014), depth EEG (Monroe et al., 1957; Schwarz et al., 1956) and PET (Vollenweider et al., 1997). Furthermore, attenuation of the subjective and behavioural effects of LSD were observed after resection of the MTLs in humans (Serafetinides, 1965) and chimpanzees (Ramey and O'Doherty, 1960).

Activation of the PHC is found during spatial navigation (Aguirre and D'Esposito, 1999; Epstein, 2008), imagining scenes (Spreng et al., 2009), emotional arousal (LaBar and Cabeza, 2006; Smith et al., 2004) and personal memory recall (Fink et al., 1996). Importantly, the PHC is also implicated in music-evoked emotion (Baumgartner et al., 2006; Gosselin et al., 2006; Koelsch, 2014) and music-evoked personal memories (Janata, 2009). Damage to the PHC can result in impaired music-evoked emotion (Gosselin et al., 2006) and visual deficits (Harding et al., 2002; Hensley-Judge et al., 2013), whereas direct stimulation of the PHC can produce visual hallucinations of scenes (Mégevand et al., 2014), autobiographical memories (Vignal et al., 2007) and dream-like states (Bancaud et al., 1994; Barbeau et al., 2005; Bartolomei et al., 2004), accompanied by enhanced coupling between the PHC and the VC (Barbeau et al., 2005).

These insights motivated the present hypothesis that LSD, in combination with music-listening, modulates PHC functional connectivity. This hypothesis was tested using functional magnetic resonance imaging (fMRI) and a balanced-order, placebo-controlled design. Participants completed ratings of eye-closed visual imagery and spontaneous autobiographical memory recollection. Acute changes in PHC functional connectivity informed a subsequent Dynamic Causal Modelling (DCM) analysis that assessed how music and LSD interact to change the direction of information flow between the PHC and the VC (i.e. effective connectivity).

[1] By the late 1960s there existed, broadly speaking, two schools of thoughts around the therapeutic use of psychedelics – and these differed in the significance they attributed to music. In the United States, higher dosages of psychedelics were administered, with the goal to facilitate a peak- or mystical-type experience to promote long lasting change in personality traits and behaviour. Here, music was typically played for the entire duration of the drug effects, with intermittent periods of silence. In Europe, *psycholytic therapy* became more widely practiced. This method involved more frequent administration of lower dosages of a psychedelic, and with more interaction between therapist and patient. Music was played for to help with relaxation, or to support intermittent periods of introspection.

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2. Experimental procedures

2.1. Approvals

This study was approved by the National Research Ethics Service (NRES) committee London – West London and was conducted in accordance with the revised declaration of Helsinki (2000), the International Committee on Harmonisation Good Clinical Practice guidelines and National Health Service (NHS) Research Governance Framework. Imperial College London sponsored the research which was conducted under a Home Office license for research with schedule I drugs.

2.2. Participants

Twenty participants (16 males and 4 females) were recruited, carefully screened for physical and mental health and provided written informed consent before participation. The screening for physical health included electrocardiogram (ECG), routine blood tests, and urine test for recent drug use and pregnancy. A psychiatric assessment was conducted and participants provided full disclosure of their drug use history. Key exclusion criteria included: being younger than 21 years of age, having a personal history of diagnosed psychiatric illness, an immediate family history of a psychotic disorder, an absence of previous experience with a classic psychedelic drug (e.g. LSD, mescaline, psilocybin or dimethyltryptamine (DMT), drug use within 6 weeks of the first scanning day, a persistent adverse reaction to a psychedelic drug, pregnancy, problematic alcohol-use (i.e. >40 units consumed per week), and/or a medically significant condition rendering them unsuitable for the study.

2.3. Study setting and overview

Screening took place at Imperial's clinical research facility at the Hammersmith hospital campus. All study days were performed at Cardiff University Brain Research Imaging Centre (CUBRIC). Eligible participants attended two study days that were separated by at least 14 days. LSD was received on one of the study days, and placebo on the other. The order of receipt of LSD was balanced across participants, and they were kept blind to this order but the researchers were not.

On scanning days, volunteers arrived at the study centre at 8:00 am, were given a detailed brief about the study day schedule, gave a urine test for recent drug-use and pregnancy, and carried out a breathalyser test for recent alcohol-use. A cannula was inserted into a vein in the antecubital fossa by a medical doctor and secured. Participants were encouraged to close their eyes and relax in a reclined position while the drug was administered. All participants received 75 μg of LSD, administered intravenously via a 10 ml solution infused over a two minute period, followed by an infusion of saline. Dosing was followed by an acclimatisation period of approximately 60 min, in which (for at least some of the time) participants were encouraged to relax and lie with their eyes closed inside a mock MRI scanner. This functioned to prepare the participants for the subsequent (potentially anxiogenic (Studerus et al., 2012)) MRI scanning experience.

Participants reported noticing subjective drug effects between 5 and 15 min post-dosing, and these approached peak intensity between 60 and 90 min post-dosing. The duration of a subsequent plateau of drug effects varied among individuals but was generally maintained for approximately four hours post-dosing. BOLD MRI scanning started approximately 120 min post-dosing, and lasted for approximately 60 min. This included a structural scan, arterial spin labelling (ASL) fMRI, and BOLD fMRI. After the MRI scanning, magnetoencephalography (MEG) scanning was performed but these findings will be reported elsewhere. Once the subjective effects of LSD had sufficiently subsided, the study psychiatrist assessed the participant's suitability for discharge.

3. Experimental design

Each fMRI scanning session involved three eyes-closed resting state scans, each lasting seven minutes. After each seven minute scan, visual analogue scale (VAS) ratings were performed in the scanner via a response-box. The music-listening scan always occurred after the first resting state (no music) scan and before a final resting-state scan (no music). The music itself was triggered by the first TR, and listened to via MRI compatible headphones (MR Confon). Two seven-minute long excerpts (A and B) were selected from the album *Yearning*, by ambient artist Robert Rich and classical Indian musician Lisa Moskow. Pre-study assessments confirmed the two excerpts to be balanced for their emotional potency. Each participant listened to both stimuli, in a balanced order across conditions. Volume-maximisation and broadband compression was carried out using Ableton live 9 software.

Prior to each scan, participants were instructed via a display screen to close their eyes and relax. Prior to the music scan, the music volume was adjusted to a level that was “as loud as possible, without being unpleasant” and then maintained for each condition. When the music ended, participants were instructed to open their eyes and rate the degree of simple visual imagery (i.e. “with my eyes closed I saw colours or geometric patterns”) and complex visual imagery (i.e. “with my eyes closed I saw complex visual imagery”) they experienced. Complex imagery was predefined as: static or dynamic images of objects or entities (e.g. plants, buildings, people or animals) and complex scenes. Items were completed on a continuous visual analogue scale from 0 (“not at all”) to 20 (“extremely intense”). Soon after the MRI scanning session was complete, participants rated some further VAS items that assessed their subjective experience during scanning. The VAS item “I saw scenes from my past” was selected for special consideration because of personal memory recollection being consistently associated with PHC functioning (Fink et al., 1996; Spreng et al., 2009), as well as a prior hypothesis inspired by previous findings (Carhart-Harris et al., 2012b) that this would be modulated by the experimental conditions.

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3.1. MRI scanner and data pre-processing

All imaging was performed on a 3T GE HDx system. For registration and segmentation of functional images, an initial 3D FSPGR anatomical scan was obtained in an axial orientation, with field of view=256 × 256 × 192 and matrix=256 × 256 × 192 to yield 1-mm isotropic voxel resolution (TR/TE=7.9/3.0 ms; inversion time=450 ms; flip angle=20°). Functional images were acquired using a gradient echo planer imaging sequence, TR/TE=2000/35 ms, field-of-view=220 mm, 64 × 64 acquisition matrix, parallel acceleration factor=2, 90° flip angle. Thirty five oblique axial slices were acquired in an interleaved fashion, each 3.4 mm thick with zero slice gap (3.4 mm isotropic voxels). The precise length of each of the BOLD scans was 7:20 min.

Preprocessing utilised a combination of AFNI (Cox, 1996), FSL (Smith et al., 2004b), Freesurfer (Dale et al., 1999) and ANTS (Avants et al., 2011). After brain extraction (Freesurfer), anatomical images were segmented into their three underlying tissue types: cerebrospinal fluid (CSF), grey matter (GM) and white matter (WM) (fast, FSL) and registered to a 2 mm MNI152 template using affine (ANTS), followed by non-linear transformation (SyN, ANTS). Anatomical images also underwent segmentation to define subcortical structures (Freesurfer).

One participant was excluded from analyses because of early termination of the scanning due to him reporting significant anxiety. Three participants were excluded from analyses due to technical problems with the sound delivery and four more subjects were discarded from the group analyses due to excessive head movement. This leaves a total of twelve participants that entered the group analyses. Principally, motion was measured using frame-wise displacement (FD) (Power et al., 2014). The criterion for exclusion for excessive head movement was subjects displaying higher than 15% scrubbed volumes when the scrubbing threshold is FD=0.5. After discarding these subjects, we reduced the threshold to FD=0.4. The between-condition difference in mean FD for the 4 subjects that were discarded was 0.286±0.185 and for the 12 subjects that were used in the analysis the difference in mean FD was 0.049±0.029 (mean FD for placebo was 0.085±0.028 and mean FD for LSD was 0.134±0.037, $p=0.0001$).

Functional images were pre-processed according to the following sequence: (1) Removal of first three volumes (2) de-spiking (3dDespike, AFNI), (3) slice time correction (3dTshift, AFNI), (4) motion correction (3dvolreg, AFNI), (5) brain extraction (bet, FSL), (6) rigid body registration to anatomical scans (nine subjects with FSL's BBR, one subject with Freesurfer's bbregister and two subjects manually), (7) transformation of functional to MNI 2 mm space, using previously calculated transformation matrix from the anatomical scans, (8) motion scrubbing using an FD threshold of 0.4, and replacement with the mean of neighbouring volumes (mean percentage of volumes scrubbed for placebo and for LSD was 0.5%±1 and 1.9%±2.2, respectively. Maximum volumes scrubbed for scan was 7.8%), (9) spatial smoothing with a Gaussian kernel of 6 mm (FWHM) (3dBlurInMask, AFNI), (10) band-pass filtering between 0.01 and 0.08 Hz (3dFourier, AFNI), and (11) linear and quadratic de-trending and regression of 9 nuisance parameters: 6 motion-related (3 translations, 3 rotations) and 3 anatomically-defined.

The anatomically defined regressors consisted of Ventricles (Freesurfer), Cerebrospinal fluid (CSF) (FSL's FAST with Freesurfer's Ventricles subtracted) and White matter (WM) (FSL's FAST with Freesurfer's subcortical grey-matter subtracted). All three masks were eroded to reduce partial volume effects and were used to extract nuisance time-series from an unsmoothed version of the pre-processed functional data. The CSF and Venticles were used to extract a single mean time-course for each mask, while WM mask was used to produce a voxelwise regressor (3dLocalStat, AFNI). Voxelwise WM regression has been found to outperform approaches using whole-brain averaged WM signal (Jo et al., 2010, 2013).

3.2. Subjective effects

A two-way repeated measures ANOVA with two factors (drug condition and music condition) was performed to test for an interaction between LSD and music on in-scanner ratings of simple and complex hallucinations. A paired one-tailed *t*-test was performed to examine between-condition differences in the post-scanner questionnaire item “I saw scenes from my past”.

3.3. Seed-based functional connectivity analysis

A bilateral PHC region of interest (ROI) was acquired from the Harvard anatomical atlas tool and used to extract PHC time series for each subject. To begin with, a general linear model (GLM) was used (FEAT, FSL) to model whole brain resting state functional connectivity with the PHC seed, with correction for autocorrelations (FILM, FSL) for each run separately. Next, a fixed-effects model was used to compare music versus non-music runs for each subject, for LSD and placebo separately. Finally, these drug effects (LSD versus placebo) were fed into a higher-level mixed effects model (FLAME1, FSL) to calculate the modulation of the effects of music by LSD on PHC functional connectivity across the brain (cluster correction threshold $z>2.3$, $p<0.05$).

3.4. Dynamic causal modelling: background and implementation

Dynamic Causal Modelling (DCM, as implemented in SPM12b) was used to estimate changes in effective connectivity. DCM is a biologically-informed modelling procedure that estimates the causal interactions (i.e. effective connectivity) between different pre-selected nodes of a network, and the changes in coupling strength between and within those nodes (extrinsic and intrinsic connections respectively) due to experimental manipulations (Friston et al., 2003). The basic architecture of a model is defined by structurally plausible and functionally-informed brain regions, whose connections are defined as either bilinear (i.e. information flow between regions) or non-linear (i.e. activity in one region modulating information flow between regions). Typically, experimental manipulations can directly affect activity in each node (as ‘driving inputs’)

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or alter the strength of coupling within or between nodes (as 'modulatory inputs').

In the present study, all six scans were concatenated in the following order: placebo no-music (NM), placebo music (M), placebo NM, LSD NM, LSD M, LSD NM. The measured BOLD time-series for the DCM were extracted as the first principal eigenvalue from a bilateral PHC and VC mask (The PHC mask was defined by Harvard-Oxford atlas, and the VC mask was defined by results of the PHC functional connectivity analysis, i.e. the occipital cluster), and adjusted for the effects of interest (i.e. main effect of music, main effect of drug, and an interaction effect - described below). Between-node connections were defined as bilinear meaning that information flow could be modulated in either direction. Three experimental inputs entered the model as modulatory inputs: a main drug effect, a main music effect, and an interaction effect of music and drug (0.5-1 0.5-0.5 1-0.5). Due to the resting-state conditions of the scanning, activity in the nodes was driven by stochastic (i.e. spontaneous) fluctuations (Li et al., 2011).

3.5. Dynamic causal modelling: Bayesian model selection

In DCM, a series of plausible models, representing competing hypotheses, are specified. Each model corresponds to a hypothesis about how observed changes in BOLD signal were caused by changes in neural activity in each network node. The different models can vary in terms of the position of driving and modulatory inputs. DCM uses a biophysical model of the hemodynamic response to predict the underling neuronal activity - and the underlying (changes in) connectivity - from the observed BOLD signal (see Figure 2D). Model estimation, or inversion, returns conditional estimates for the changes in connectivity and scores the model in terms of its accuracy and complexity (using a Free Energy bound on log model evidence). Bayesian Model Selection (BMS) is used to compare different models to identify the model with the greatest evidence - i.e. the model that offers the best explanation of the data. In the present study, one "full model" was specified, with all three experimental inputs modulating all extrinsic and intrinsic connections. Following inversion of this full model, a post hoc Bayesian model optimisation scheme was used to identify the model structure with the greatest model evidence (i.e. lowest free energy). This approach provides an efficient scheme for scoring large numbers of competing models (Friston and Penny, 2011). Optimal model structure is usually determined by computing Bayes factors, as an approximation of the model evidence. A Bayes factor of 20 corresponds to a belief of 95% in the statement that a particular hypothesis (i.e. the proposed model) is true, and therefore a p-value of 0.05. A Bayes factor higher than 150 corresponds to a belief of 99% in the hypothesis, and equates a p-value smaller than 0.01. A Bayes factor higher than 20 is therefore considered as strong evidence for the proposed model (Penny et al., 2004). After model selection, coupling parameters are analysed post-hoc to characterize the size and direction of the changes in connection strength caused by the experimental manipulations. Coupling parameters quantify the strength of the coupling in terms of the rate (in Hz) at which a response is caused in a given region, and modulation is expressed as either an increase or decrease in this coupling measure.

3.6. Correlations with subjective effects

Following model selection, the hypothesis was tested that the magnitude of the modulation in effective connectivity by the music $\times$ drug interaction would explain the observed variance in participants' subjective responses to the music under LSD. More specifically, we asked whether the size of the interaction effect as estimated by the DCM, correlated with the magnitude of the enhancement of (1) eyes-closed imagery and (2) visions of one's past ("I saw scenes from my past"). A spearman's correlation was used due the non-parametric nature of the data.

4. Results

4.1. Participant demographics

The data from twelve participants were found suitable for data-analysis (2 female, mean age=33$\pm$9 years, range 22-47 years). All had at least one previous experience with a classic psychedelic drug. Mean estimated lifetime LSD-use was 12$\pm$15 (range=0-40). Self-estimates of other drug-use were as follows (mean$\pm$SD, range): weekly alcohol units=8$\pm$8, 0-28; daily cigarettes=0; lifetime cannabis uses=686$\pm$625, 30-2000; lifetime MDMA uses=20$\pm$18, 2-50; lifetime psilocybin/magic mushroom uses=10$\pm$9, 1-35; lifetime ayahuasca/DMT uses=14$\pm$21, 0-50; lifetime ketamine uses=3$\pm$6, 0-20; lifetime cocaine uses=6$\pm$8, 0-20; lifetime amphetamine uses=6$\pm$11, 0-35; lifetime heroin uses=1$\pm$3, 0-10.

4.2. Subjective effects

A paired t-test revealed a significant increase in personal memory recollection under LSD (t=1.9, df=19, p=0.04). For simple hallucinations, a two-way ANOVA revealed a significant drug effect (F=42.2, df=18, $p<0.001$) but no significant effects were found for music (F=1.7, df=18, p=0.2) or the interaction between music and LSD (F=1.1, df =18, p=0.3). For complex hallucinations, a two-way ANOVA revealed a significant drug effect (F=24.7, df=18, $p<0.001$), a trend level effect of music (F=10.0, df=18, p=0.09), but again, no significant interaction effect for music $\times$ LSD (F=1.8, df=18, p=0.5). Drug effects on simple and complex hallucinations survived multiple comparisons, using Bonferroni adjusted alpha levels of 0.025 per test (0.05/2).

4.3. Functional connectivity

Seed-based functional connectivity analysis of the bilateral PHC showed a positive interaction between music and LSD for the contrast LSD (music versus no music) versus placebo (music versus no music), with increased coupling between the PHC and two main clusters: One being the bilateral visual cortex and the other being the left inferior frontal gyrus (see Table 1 and Figure 1a). No decreases in PHC

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Table 1 Brain regions showing increased coupling with the parahippocampus.

Cluster	Region	Lateralization	Size (mm)	Peak z-score	Peak coordinates (mm)
Occipital	Calcarine fissure	L	3722	4.02	8, −76,8
	Calcarine fissure	R	4516	4.02	6, −84,8
	Cuneus	L	4190	3.62	4, −80,6
	Cuneus	R	2732	3.44	−8, −88,10
	Lingual cortex	L	4600	3.29	6, −78,4
	Lingual cortex	R	3052	3.28	−6, −76,20
	Superior occipital gyrus	L	5036	3.07	26, −78, −2
	Fusiform gyrus	R	2848	2.74	12, −70,22
Inferior frontal	Middle frontal cortex	L	3380	3.52	−30,32, −8
	Inferior frontal gyrus, opercular	L	5058	3.47	−44,36,22
	Inferior frontal gyrus, triangularis	L	9726	3.33	−42,38,22
	Precentral gyrus	L	7052	3.28	−56,2,28
	Inferior frontal gyrus, orbitalis	L	2076	3.27	−44,12,18
	Insula	L	3716	3.11	−32,22,14

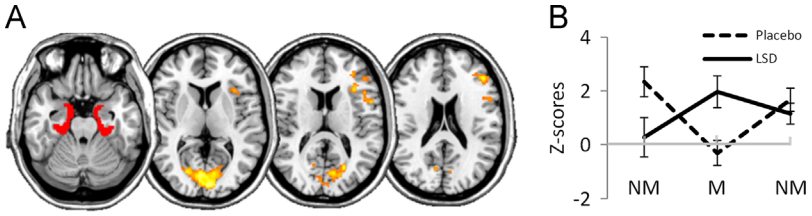

Figure 1 Seed-based functional connectivity analysis of the bilateral parahippocampus. (A) Brain regions showing increased coupling (displayed in yellow, cluster-corrected, $Z>2.3$) with the bilateral PHC (displayed in red) for the contrast LSD (music > no music) > placebo (music > no music) (the left side of the brain is shown on the right side of the brain in these images, as if the body is being viewed through the soles of the feet). Significant effects were observed in the primary visual cortex, left anterior insula, and left inferior frontal cortex. (B) Coupling between the PHC and the visual cortex under LSD and placebo (NM=No Music, M=Music) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

functional connectivity were observed for this contrast. A two-way repeated-measures ANOVA on z-scores for the VC did not show a significant effect of drug ($F=0.49$, df=11, $p=0.5$) or music ($F=2.27$, df=11, $p=0.16$), but did reveal an interaction effect of music and LSD ($F=17.04$, df=11, $p=0.002$) (see Figure 1b. for a plot of the z-scores).

4.4. Dynamic causal modelling

Post-hoc model optimisation determined the optimal model structure. The optimal model had a Bayes factor 344 higher than the preceding model architecture. This equates, in a frequentist statistical approach, to a p-value much smaller than 0.01, and is therefore considered as strong evidence for the model. The optimal model features a main effect of drug and music modulating the intrinsic connections of both nodes, and an interaction effect modulating the connection from the PHC to the VC. Group averages for the posterior estimates are -0.41 ± 0.05 Hz for drug effect on PHC, -0.42 ± 0.06 Hz for music effect on PHC, -0.38 ± 0.06 Hz for drug effect on VC, and -0.40 ± 0.06 Hz for music effect on VC. The group average of the posterior estimate for the interaction effect is 0.02 ± 0.04 Hz (Table 2).

4.5. Correlations

A significant positive correlation was found between the interaction effect of LSD and music on PHC to VC effective connectivity, and increases in the in-scanner ratings for complex visual imagery (Spearman's $\rho=0.71$, with $p=0.01$, and Pearson $r=0.65$, with $p=0.03$). A trend-level positive correlation was found between the interaction effect of LSD and music on PHC to VC, and the post-scanner questionnaire item "I saw scenes from my past" (Spearman $\rho=0.67$, with $p=0.02$, and Pearson $r=0.69$, with $p=0.01$). These tests were conducted using Bonferroni adjusted alpha levels of 0.0167 per test (0.05/3) (see Figure 3).

5. Discussion

The present study has demonstrated that increased PHC-VC effective connectivity during music-listening under LSD correlates with enhancements in eyes-closed mental-imagery. These results are consistent with current thinking on the role of the PHC in mental imagery, and provide new insights into the brain mechanisms by which psychedelics

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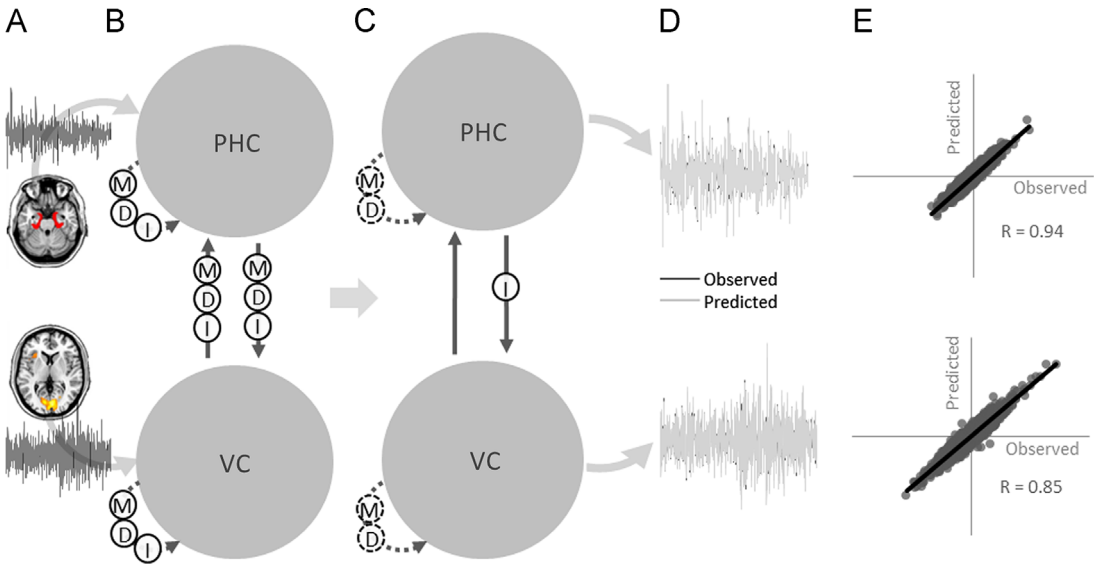

Figure 2 Dynamic Causal Modelling. (A) Time series that enter the DCM are extracted as first principal eigenvalues from the PHC mask and the VC mask (the latter is defined by the seed-based functional connectivity result) (Dale et al., 1999). The full DCM that enters the Bayesian model selection (BMS) after model estimation. The model has two nodes (PHC and VC) that are connected via extrinsic bilinear connections, and each node has one intrinsic connection. Every connection has three modulatory effects: D=main drug effect, M=main music effect, I=Interaction effect. The nodes are driven by stochastic fluctuation. (C) Post-hoc model optimisation determined the optimal model structure. Dashed lines indicate a negative connection or modulation, whereas normal lines indicate a positive connection or modulation. This model has the main effect of drug and the main effect of music modulating the intrinsic-connections of both nodes. The interaction effect has a modulatory effect on the connection from PHC to VC. (D) The sum estimated neural activity in each node is convolved by the hemodynamic response function to yield a predicted BOLD response. The predicted BOLD response is compared to the observed BOLD response to determine how well the model explains the data. Displayed are predicted and observed time-series from one subject for illustration purposes. (E) Scatterplots illustrate model fit by correlation of predicted verses observed BOLD responses for both regions.

Table 2 Pearson correlation coefficients from all participants for predicted versus observed BOLD signals for visual cortex (VC) and parahippocampus (PHC).

Participant	VC	PHC
1	0.95	0.94
2	0.91	0.97
3	0.89	0.91
4	0.92	0.95
5	0.88	0.93
6	0.91	0.93
7	0.97	0.95
8	0.82	0.87
9	0.93	0.90
10	0.92	0.96
11	0.88	0.86
12	0.85	0.94

may enhance some of the subjective effects of music-listening.

The PHC is implicated in the generation of visual mental imagery (Brewer et al., 1998; Epstein, 2008), personal memory recollection (Fink et al., 1996; Spreng et al., 2009) and music-evoked personal memories (Janata, 2009). Within the MTL system, the PHC primarily functions to encode and retrieve context-related memory content (Ranganath and Ritchey, 2012), which is consistent with complex rather than simple visual imagery. Direct structural (Catani et al., 2002) and functional (Libby et al., 2012; Powell et al., 2004) connections between the PHC and the VC have been detected, and increased information flow from the PHC to the VC (i.e. effective connectivity) has previously been found to occur during the construction of visually imagined scenery (Chadwick et al., 2013). Interestingly, direct stimulation of the PHC can produce visual hallucinations of complex scenes (Mégevand et al., 2014) and autobiographical memories (Bancaud et al., 1994; Bartolomei et al., 2004), and there is evidence that this is related to a strengthening of PHC-VC coupling (Barbeau et al., 2005). Damage to the PHC can result in visual neglect (Hensley-Judge et al., 2013) visual hallucinations (Harding et al., 2002) and hippocampal damage has been linked to an impaired ability to imagine complex scenes (Cooper et al., 2011).

In sum, these findings suggest that PHC-VC effective connectivity constitutes an important pathway for the construction of visual imagery (Chadwick et al., 2013; Zeidman et al., 2014). Mechanistically, increased information flow from the PHC to the visual cortex may correspond to an increase in top-down (prior) information (instantiated by PHC activity) being conferred on activity in the lower levels of the visual system (that normally processes incoming visual information) (Aguirre and D'Esposito, 1999; Libby et al., 2012; Summerfield et al., 2006). The present study has shown that the combination of LSD and music modulates information flow from the PHC to the VC, and that the

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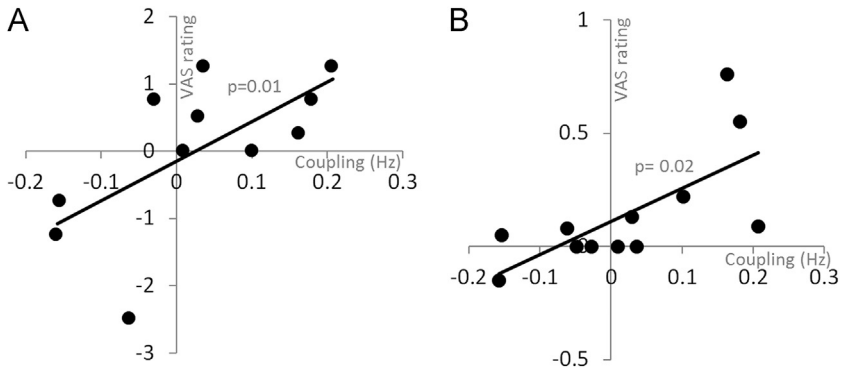

Figure 3 Correlation analyses suggest that the interaction between LSD and music induces certain subjective experiences via increasing the influence of PHC activity on VC activity. Changes in coupling parameters are displayed on the *x*-axis and are significantly correlated with: (A) increases in complex visual imagery (*Y*-axis) (i.e. music > rest for LSD > placebo) and (B) increases in visions of one's personal past (*Y*-axis) (i.e. LSD > placebo).

magnitude of this modulation predicts enhanced visual imagery. Importantly, this correlation was only evident for the complex visual imagery item (defined as the eyes-closed hallucinations of objects, entities and scenes), and not for simple imagery (defined as low-level visual features such as colours and patterns). We therefore propose that the experience of perceiving complex imagery whilst listening to music under LSD may be the result of an enhanced gain on circuits (such as the PHC to VC circuit) that normally confer complex, top-down information about (a potential) visual scene. Perceiving complex scenes in the absence of visual input may therefore result from a "flip" in the normal direction of information flow within the visual system such that higher-level components of the system, responsible for processing high-level features, take precedence over incoming sensory information.

The PHC possesses high baseline connectivity with high-level cortical regions such as those that make-up the so-called default-mode network (Raichle et al., 2001; Ward et al., 2014). Under normal conditions, the top-down inhibitory control over PHC activity is provided by projections from the posterior cingulate cortex (PCC), the retrosplenial cortex (RSC) and the medial prefrontal cortex (mPFC), that terminate on interneurons within the PHC (Mohedano-Moriano et al., 2007; Morris et al., 1999; Vann et al., 2009). The RSC, PCC and mPFC express notably high levels of serotonin 2A receptors (Erritzoe et al., 2009), and psychedelics have a dysregulating effect on activity within these regions (Carhart-Harris et al., 2012a; Muthukumaraswamy et al., 2013). The dysregulating effect of psychedelics on activity in these cortical regions may compromise their ability to maintain top-down control over the PHC. Indeed, reduced functional connectivity between the PHC and the RSC has been observed after both psilocybin and LSD (Carhart-Harris et al., 2014). Thus, the effects of psychedelics on the PHC's inhibitory afferents may increase its sensitivity and responsiveness to stimuli that normally engage it, such as music (Koelsch, 2014; Mitterschiffthaler et al., 2007; Trost et al., 2012) or odour (Jung et al., 2006).

Effects of sound on eyes-closed visual experiences under LSD have been reported since its discovery. Albert Hoffman, who discovered the powerful psychoactive effects of LSD by accidentally intoxicating himself, describes his experience in his memoir (Hoffman, 1970): "It was particularly remarkable how every acoustic perception, such as the sound of a door handle or a passing automobile, became transformed into optical perceptions. Every sound generated a vividly changing image, with its own consistent form and colour." Such experiences are often compared to synaesthesia, a neurological condition characterized by involuntarily sensory experiences (for example seeing a colour) in response to a different sensory stimulus (for example, hearing a sound). Synaesthesia is characterized by responses that are consistent to a specific stimulus (Ward, 2013), and it is therefore not possible to say to what extent the audio-visual experiences reported under LSD can be formally be termed "synesthetic" in the conventional sense. The present results do, however, suggest a plausible mechanism via which such experiences can arise, and highlight how psychedelics can inform on the neuroscience of sensory processing.

5.1. Implications for psychedelic-assisted psychotherapy

Music is an effective medium for evoking emotion (Trost et al., 2012) and autobiographical memories (Janata, 2009; Janata et al., 2007) and these effects of music have been therapeutically exploited (Castillo-Pérez et al., 2010; Erkkilä et al., 2011). Music may serve to deepen the psychedelic experience by enhancing emotional engagement (Kaelen et al., 2015) and stimulating personally meaningful mental imagery (Carhart-Harris et al., 2012b). The findings of the present study help to elucidate the mechanisms by which music and psychedelics can do this but further research is required to test its therapeutic value directly.

5.2. Limitations

No interaction was found between LSD and music on in-scanner subjective ratings, whereas connectivity analyses did show a significant interaction effect on PHC-VC coupling. Since enhanced PHC-VC coupling via the interaction between LSD and music correlated with complex mental imagery, this could be explained by individual differences in

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subjective response to LSD and music, and perhaps appraisal of the subjective experience. For example, it may have been the case that some participants disliked the genre of music or were distracted by the considerable ambient noise emitted by the MRI machinery. Some participants may also have been emotionally relaxed by the particular music that was chosen, rather than emotionally stimulated. Further work is required to test these different hypotheses. For example, a study could be designed that incorporates more than one genre of music (e.g. emotionally relaxing music versus emotionally evocative and/or arousing music). Finally, the present results cannot be extrapolated to a patient population, in which the music × psychedelic interaction is thought to be especially important (Bonny and Pahnke, 1972; Kaelen et al., 2015). Subsequent work is therefore needed to further our understanding of how music and psychedelics interact and how this may be useful for psychedelic-assisted therapy.

6. Conclusions

The present study revealed a positive interaction between LSD and music on PHC functional and effective connectivity. More specifically, a modulation of PHC to VC connectivity was observed that correlated positively with eyes-closed visual imagery, and particularly imagery of a complex and autobiographical nature. These results extend our understanding of circuitry involved in visual imagery and suggest how LSD and music can work in synergy to enhance this phenomenon. The present results provide the beginnings of a mechanistic explanation for the role of music listening in psychedelic drug-assisted psychotherapy; however, a large amount of work is required to develop our understanding of whether and how psychedelic-assisted psychotherapy can be effective.

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Contributors

MK designed and coordinated the study, carried out data collection, undertook data analyses and wrote the first draft of the manuscript. LR, JK, ASR, CO and RL undertook data analyses. MB, TW and LW carried out data collection. FSB, MBW, AF helped designing the study.SM and DJN helped designing and coordinating the study. RCH designed and coordinated the study, and carried out data collection and writing of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Author MBW's primary employer is Imanova Ltd., a private company that performs contract research work for the pharmaceutical and biotechnology industries. All other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.euroneuro.2016.03.018.

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